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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,365	10/20/2008	Morten Albrechtsen	ALBRECHTSEN2	2440

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EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,365	ALBRECHTSEN ET AL.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,14,17-32,35,36 and 39* is/are pending in the application.

4a) Of the above claim(s) *22-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,12,17,20,21,35 and 39* is/are rejected.

7)☒ Claim(s) *14,18,19 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/27/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. Claims 1, 11, 17-20, 35 and 36 have been amended and claims 4-10, 15, 16, 37, 38 and 40-49 have been canceled as requested in the amendment filed November 8, 2010. Following the amendment, claims 1, 11, 12, 14, 17-32, 35, 36 and 39 are pending in the current application.

2. Claims 22-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions or sequences, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 14, 2010.

3. Claims **1, 11, 12, 14, 17-21, 35, 36** and **39** are under examination in the present office action.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed December 27, 2010 has been considered and the references therein are of record.

Withdrawn Objection and Rejections

5. Any objection or rejection of record pertaining to any of claims 4, 5, 15, 16, 37, 38 or 40-49 is rendered moot on account of Applicants' cancellation of said claims.

6. Applicant's submission of a corrected sequence listing, filed November 15, 2010, has been accepted and is of record. Accordingly, the objection to the specification set forth at paragraph 7 of the previous office action (mailed 08/31/2010), is withdrawn.

7. The objection to claim 20, for containing an undefined acronym (i.e., LPA) , is withdrawn in view of Applicants' amendment to the claim.

8. The rejection of claims 1, 20, 21 and 39 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, set forth at paragraph 16 of the previous office action, is withdrawn in view of Applicants' amendments to the claims.

Maintained Objections and Rejections

Specification

6. The objection to the Abstract of the Specification set forth at paragraph 6 of the previous office action is maintained for reasons of record. Applicants are commended for their attempt to rewrite the Abstract (filed with the response on November 8, 2010), and the Examiner regrets any confusion Applicants may have had in determining what the objection was for. Specifically, the abstract contains legal phraseology often used in patent claims, such as "said", wherein such language should be avoided. Applicant is respectfully invited to amend the abstract to omit such language.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 11, 12, 17, 20, 21, 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 03/016351 by Kiselyov et al. in view of WO 00/18791 by Holm. The rejection is maintained for reasons of record and as discussed below.

Response to Arguments

9. In the response filed November 8, 2010, Applicants argue that while the WO document by Kiselyov et al. teaches the sequence of SEQ ID NO: 1 (which corresponds to the instant SEQ ID NO: 1), the preferred embodiments are as a monomer or a multimeric compound (a dendrimer) comprising four peptide sequences linked to a lysine backbone. Dimers, Applicants allege, are mentioned as a less preferred alternative structure, and the document does not disclose any particular dimeric compounds comprising SEQ ID NO: 1 nor a dimer consisting of two copies of SEQ ID NO: 1. Applicants further assert that Kiselyov does not teach a linker of the formula X[(A)nCOOH] [(B))mCOOH] as required by the present claims, nor does the document suggest such compounds as advantageous for FGFR binding and treatment of FGFR related diseases.

With respect to the WO 00/18791 document by Holm, Applicants argue that this document discusses technical advantages of using an LPA assembly method in relation to methods known in the art, but does not discuss or present any data showing that a dimeric compound obtained by this production method is advantageous in comparison with either a single presentation of a particular biologically active amino acid sequence or in comparison with another dimeric compound comprising the same particular amino acid sequence obtained by another method.

Applicants assert that the FGL (SEQ ID NO: 1) dimeric peptides of the present invention have an improved effect over the individual monomers of Kiselyov (e.g., they are 200 times more potent than monomeric FGL in promotion of neurite outgrowth).

Additionally, Applicants submit that only FGL peptide dimers produced by the LPA method described in WO 00/18791 (Holm) retain functional activity, as opposed to dimers linked by various other methods (e.g., FGL_{Lys}, FGL_{Cys}; see Figure 10). Applicants assert that this finding is surprising and could not have been foreseen from the prior art. In particular, Applicants argue that there is no reference or motivation in Kiselyov to make use of the peptide linkers disclosed by Holm, and vice versa. Because a variety of methods for producing peptide dimers or fusion proteins were available to the skilled person, Applicants contend that the skilled artisan would not have been able to predict from Kiselyov with any kind of certainty that only dimers of SEQ ID NO: 1 produced using the linker defined in claim 1 and Holm would have the desired biological effect, while having the desired homogeneity required for a pharmaceutical composition. Applicants further assert that the surprising finding of the present invention is that only a dimer produced by the LPA method maintains the capability of binding to FGFR, even with enhanced effect; this could not have been foreseen by the prior art. Therefore, Applicants argue that the examiner has used improper hindsight reasoning to state that it would have been obvious that the LPA method would be useful in the present invention.

10. Applicants arguments have been fully considered but they are not persuasive. With respect to the WO document by Kiselyov, it is noted that even though there are no working examples of dimers disclosed in the reference, Kiselyov clearly contemplates the use of dimers, wherein the dimers may comprise identical or non-identical monomers (see p. 25). While these are not “preferred embodiments” of Kiselyov’s

disclosure as Applicants have stated, dimers comprising SEQ ID NO: 1 are still encompassed by the teachings of Kiselyov and would have been recognizable by the ordinarily skilled artisan. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005). Apart from the inclusion of the specific linker of claim 1, Kiselyov's disclosed peptide compounds are on point to the functional activity (i.e., compounds capable of binding FGFR and inducing neurite outgrowth/ neuronal survival) and intended use (treatment of FGF-related conditions and diseases) of the presently claimed invention. There is nothing in Kiselyov to indicate, for example, that dimeric compounds are less desirable than monomeric or multimeric (dendrimeric) compounds, or that dimeric compounds would not function as intended. In fact, Kiselyov explicitly teaches that for pharmaceutical compositions, multimers or *dimers* are preferred (see p. 26, line 6). Therefore, having read the disclosure by Kiselyov, the ordinarily skilled artisan would have fair reason to expect that any of the disclosed compounds, such as dimeric compound comprising the peptide of SEQ ID NO: 1, would be capable of performing as desired, such as for therapeutic purposes.

Moreover, in determining the scope and content of the prior art at the time of filing, the ordinarily skilled artisan would have been aware that multiple presentation of peptide sequences is a valuable means to amplify biological responses of peptide

sequences (as indicated at p. 3, lines 19-23 of the instant specification in reference to the prior art). For example, WO 01/96364 by Saffell (reference "AK" listed on 12/27/2010 IDS) demonstrates that certain peptides derived from NCAM (which is the same molecule from which the instant SEQ ID NO: 1 is derived) cannot stimulate neurite outgrowth as monomers, but can do so as multimers (see paragraph spanning pp. 26-37). The present application's finding that dimers of SEQ ID NO: 1 are more potent than monomers is thus hardly surprising. It is also noted that dimeric compounds according to instant claim 1 (e.g., FGL_L) are no more potent at stimulating neurite outgrowth than tetrameric (dendrimeric) FGL compounds (FGL_d) (compare, for example, Fig. 9 showing FGL_d effects to Fig. 10 showing FGL_L effects). Therefore, the only potential source of uniqueness for the present invention is the linker molecule which, coincidentally, is the only thing not taught by Kiselyov but is described in full by Holm.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, Kiselyov teaches the use of dimeric compounds comprising a peptide of SEQ ID NO: 1,

and Holm teaches improved production methods for assembling dimeric and multimeric peptide compounds. The skilled artisan would have been aware, for example, that Holm's LPA method of preparing polyfunctional constructs (i.e., dimers, multimers) was advantageous because it was easier to use than the other standard methods of peptide preparation, more versatile due to its ability to include non-identical sequences, and more reproducible, thus allowing for higher purity of the resulting compound. This alone is sufficient motivation to use the LPA method disclosed by Holm, which would include the use of achiral linker molecules such as those recited in claim 1, instead of other standard linkers and assembly methods in the production of dimeric molecules comprising SEQ ID NO: 1 as taught by Kiselyov.

Furthermore, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Accordingly, the combined teachings of the Kiselyov and Holm references still render obvious the present invention recited in claims 1, 11, 12, 17, 20, 21, 35 and 39.

Conclusion

11. Claims 1, 11, 12, 17, 20, 21, 35 and 39 are rejected. Claims 14, 18, 19 and 36 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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